ATTACHMENT A

REMARKS

Claims 1-55 stand pending in the present application with claims 1-43 being withdrawn from consideration. By this Amendment, Applicants have amended claim 44. This amendment does not reflect any new issues since the claims as originally filed already recited that the kit actually includes gas (see original claim 1, "*a biocompatible fluid adhesive protein foam. . .characterized in that it comprises a biocompatible fluid adhesive protein matrix which is bioresorbable and non toxic, containing a biocompatible* ***and*** *non toxic gas or mixture of gases*"). Since the amendment raises no new issues and place the claims in condition for allowance, the amendment should be entered. Applicants respectfully submit that upon entrance of the present amendment, the present application will be placed in condition for allowance based on the arguments set forth below.

Claims 44-54 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Stroetman in view of Wycech et al (hereinafter "Wycech").

Contrary to the Examiner's assertion, the present invention is not made obvious by Stroetman in view of Wycech. As described in great detail in the prior Amendment of March 26, 2003, novelty of the present invention lies in part in a kit which provides a biocompatible fluid adhesive protein foam as a dry preparation having a foam-like and fleece-like structure obtained in a ready to use form. The Examiner has failed to address Applicants' distinguishing feature that the present adhesive is obtained in a "ready to use" form. As discussed in the prior Amendment, the added feature that the protein foam be present in a foam is not taught nor suggested by the prior art of record

which includes Stroetman and now Wycech. Moreover, the prior amended claim 44 excludes prior kits requiring preparing a foam which requires further processing, molding or freeze drying before use. In fact, the present kit allows the protein foam to be used, *in situ*, i.e., to be directly applied on biological tissue or the implanted material. Thus, the prior art kits which produce a protein product requiring further processing fail to teach or suggest the claimed kit.

In sharp contrast to the present, as well as formerly claimed kit, the preparation disclosed by Stroetman is not suitable for preparing a composition in a ready to use form as claimed. In fact, the Stroetman formulation must be deep frozen and, as a result, the Stroetman kit also requires a mold (see Stroetman, column 15). Moreover, the kit of Stroetman does not enable direct application of the formulation on biological tissue or an implanted biomaterial.

Furthermore, Stroetman requires further processing steps which are incompatible with the claimed ready to use foam. As noted above, the presently claimed kit allows the *in situ* preparation of an adhesive foam in a ready to use form without any further steps in view of the fact that biological tissues are involved. In sharp contrast to this claimed feature, Stroetman requires deep-freezing. These steps are incompatible with the claimed direct application on biological tissues.

Wycech is not analogous art and therefore not relevant to the present invention as Wycech. Wycech is directed to a system for reinforcing a hollow structure member of a motor vehicle whereas the present invention is directed to a biological protein structure and Stroetman is directed to a fibrinogen-containing dry preparation (Wycech, column 1, line 13). Therefore, Wycech is non-analogous art to that of Stroetman and

the present invention. Moreover, Wycech has nothing to do with an adhesive protein foam to be applied to biological tissues as claimed. Therefore, it is inappropriate to combine Wycech with Stroetman in an obviousness-type rejection as Wycech is not analogous art.

Moreover, the composition disclosed in Wycech requires kneading and heat treatment (Wycech, column 12, line 6 and column 12, line 27) which clearly are unsuitable for direct application on biological tissues as claimed. Further, the further processing is incompatible with the claimed ready to use form.

Further, both Stroetman and Wycech fail to teach or suggest a kit that is designed for preparing a fluid foam as claimed. The composition disclosed by Stroetman is directed to a solid as it is deep frozen and lyophilized. Similarly, Wycech does not disclose a fluid foam as claimed but instead discloses a dough-like composition (Wycech, column 12, line 11). Consequently, the kits inherently disclosed by Stroetman and Wycech are not suitable for preparing the fluid composition of the claimed invention. As a result, the present fluid foam is not taught nor suggested by Stroetman or Wycech individually or in combination with one another.

In an effort to more clearly and succinctly recite the present invention, Applicants have amended independent claim 44 to more clearly recite that the presently claimed kit requires a gas in addition to two reagents together with the reagents in either the first or second container or the gas may be present alone in a third container. Subject matter basis for the current amendment to claim 44 can be found in the claims as previously presented, including the claims dependent from claim 44. Consequently the subject matter now recited in claim 44 has already been considered in prior Office Actions.

Accordingly, the amendment to claim 44 is proper and should be entered after final and in no way does the amendment to claim 44 raise new issues.

It is respectfully submitted that none of the prior art documents of record discloses a kit comprising a gas. Wycech discloses a two-part kit without reference to any gas (see Wycech, column 1). The process for preparation of the composition of Stroetman only requires fibrinogen and thrombin without including the use of a gas. As a result, none of the cited art of record provides any guidance for one of ordinary skill in the art to provide a kit for preparing a fluid foam for biological use from a protein compound, a cross-linking polymerization compound and a gas.

In conclusion, none of the above three distinguishing features, i.e., fluid foam, biological use, or a gas, is taught or suggested in the prior art. Therefore, the present claims are novel and not obvious from the prior art of record.

Based on the foregoing discussion, Applicants respectfully request that upon entrance of the present amendment, the rejections to claims 44-54 under 35 U.S.C. § 103(a) will be overcome and should be withdrawn.

In view of the forgoing Applicants respectfully submit that the present application is in condition for allowance.

END REMARKS

ATTACHMENT B
Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application.

1. (Withdrawn) A biocompatible fluid adhesive protein foam, which is bioresorbable and nontoxic, for surgical and/or therapeutic use, in particular for protecting/cicatrizing tissue wounds and for attaching biological tissues to each other or to an implanted biomaterial, characterized in that it comprises a biocompatible fluid adhesive protein matrix, which is bioresorbable and nontoxic, containing a biocompatible and nontoxic gas or mixture of gases.

2. (Withdrawn) The adhesive foam as claimed in claim 1, characterized in that the adhesive matrix consists of, or comprises, an at least partially polymerized/crosslinked protein compound which is nontoxic, biocompatible and biodegradable and which has adhesive properties, said protein compound optionally being chemically modified.

3. (Withdrawn) The adhesive foam as claimed in claim 1, characterized in that the protein compound consists of, or comprises, a protein or a mixture of proteins selected from collagen, gelatin, albumin, elastin and fibrinogen, preferably from collagen and albumin.

4. (Withdrawn) The adhesive foam as claimed in claim 1, characterized in that the protein compound consists of, or comprises, collagen.

5. (Withdrawn) The adhesive foam as claimed in claim 4, characterized in that the protein compound consists of, or comprises, native collagen, native collagen which is chemically modified, especially by methylation, by succinylation or by oxidative cleavage in particular with the aid of periodic acid or a salt thereof, native collagen without telopeptides or nonhydrolyzed collagen which has at least partially lost its helical

structure, consisting mainly of α chains the molecular weight of which is close to 100 kDa (heated collagen).

6. (Withdrawn) The adhesive foam as claimed in claim 4, characterized in that the protein compound consists of, or comprises, heated collagen.

7. (Withdrawn) The adhesive foam as claimed in claim 1, characterized in that the protein compound is crosslinked with a reactive polymer of molecular weight higher than 1000, preferably selected from macromolecular polyaldehydes and hydrophilic polymers capable of reacting with the protein compound, in particular with respect to amine or sulfhydryl functions.

8. (Withdrawn) The adhesive foam as claimed in claim 7, characterized in that the macromolecular polyaldehyde is selected from oxidized polysaccharides or mucopolysaccharides, preferably from starch, dextran, agarose, cellulose, chitin, chitosan, alginic acid, glycosaminoglycans, hyaluronic acid and chondroitin sulfate, and the derivatives or mixtures thereof, more preferably from starch, dextran and hyaluronic acid.

9. (Withdrawn) The adhesive foam as claimed in claim 8, characterized in that the macromolecular polyaldehyde comprises oxidized starch.

10. (Withdrawn) The adhesive foam as claimed in claim 7, characterized in that the hydrophilic polymer is chosen from derivatives of poly(ethylene) glycol (PEG), poly(oxyethylenes), poly(methylene glycols), poly(trimethylene glycols) and poly(vinylpyrrolidones), derivatives of PEG being the most preferred.

11. (Withdrawn) The adhesive foam as claimed in claim 1, characterized in that the adhesive matrix consists of, or comprises, heated collagen crosslinked with oxidized starch.

12. (Withdrawn) The adhesive foam as claimed claim 1, characterized in that the adhesive matrix consists of, or comprises, albumin crosslinked with oxidized starch.

13. (Withdrawn) The adhesive foam as claimed in claim 1, characterized in that the adhesive matrix consists of, or comprises, albumin crosslinked with a reactive polymer.

14. (Withdrawn) The adhesive foam as claimed in claim 1, characterized in that the adhesive matrix consists of, or comprises, a fibrin glue.

15. (Withdrawn) The adhesive foam as claimed in claim 1, characterized in that the gas is selected from air, nitrogen, oxygen and carbon dioxide or the mixture of one or more of these gases, preferably from air, carbon dioxide and nitrogen, air being most particularly preferred.

16. (Withdrawn) The adhesive foam as claimed in claim 1, characterized in that the volume of gas represents 25 to 90% of the total volume of the foam, preferably 40 to 75%.

17. (Withdrawn) The adhesive foam as claimed in claim 1, characterized in that the foam contains one or more biologically active substances.

18. (Withdrawn) The adhesive foam as claimed in claim 1, characterized in that it is tightly attached to a collagen film.

19. (Withdrawn) A process for producing a biocompatible fluid adhesive protein foam, which is bioresorbable and nontoxic, for surgical and/or therapeutic use, in particular for protecting/cicatrizing tissue wounds and for attaching biological tissues to each other or to an implanted biomaterial, characterized in that it comprises extemporaneously mixing, in a homogeneous manner, a protein compound which can be polymerized/crosslinked, and which is potentially adhesive, with a polymerization/crosslinking agent so as to form a fluid biocompatible adhesive protein

matrix material, which is bioresorbable and nontoxic, and a biocompatible and nontoxic gas or mixture of gases with this fluid adhesive protein matrix material or with one of the basic constituents of such a material solubilized in aqueous medium.

20. (Withdrawn) The process as claimed in claim 19, characterized in that the protein compound in solid form, in particular in the form of fibers or of dry powder, is mixed extemporaneously with a buffered aqueous solution with the aid of heating means, and in that the polymerization/crosslinking agent is supplied to the mixture.

21. (Withdrawn) The process as claimed in claim 19, characterized in that the protein compound consists of, or comprises, a protein or a mixture of proteins selected from collagen, gelatin, albumin, elastin and fibrinogen, preferably from collagen and albumin.

22. (Withdrawn) The process as claimed in claim 19, characterized in that the protein compound consists of, or comprises, native collagen in the form of an aqueous solution at a concentration of between 1 and 5%, preferably 2.5 and 4% by weight.

23. (Withdrawn) The process as claimed in claim 19, characterized in that the protein compound consists of, or comprises, heated collagen solubilized in aqueous medium at a concentration of between 4 and 20%, preferably between 5 and 18% by weight.

24. (Withdrawn) The process as claimed in claim 19, characterized in that the protein compound consists of, or comprises, albumin solubilized in aqueous medium at a concentration of between 20 and 50%, preferably 40 to 50%.

25. (Withdrawn) The process as claimed in claim 19, characterized in that the polymerization/crosslinking agent is a reactive polymer of molecular weight higher than 1000, preferably selected from macromolecular polyaldehydes and hydrophilic polymers capable of reacting with the protein compound, in particular with respect to amine or sulfhydryl functions.

26. (Withdrawn) The process as claimed in claim 25, characterized in that the polymerization/crosslinking agent is a macromolecular polyaldehyde solubilized in aqueous medium at a concentration of between 0.5 and 10% by weight, preferably between 1 and 3% by weight.

27. (Withdrawn) The process as claimed in claim 19, characterized in that the protein compound consists of, or comprises, native collagen or heated collagen, and the polymerization/crosslinking agent is oxidized starch.

28. (Withdrawn) The process as claimed in claim 19, characterized in that the proportion of macromolecular polyaldehyde to heated collagen is 1/10 to 1/160, preferably 1/15 to 1/50, the mixing temperature being between 35°C and 41°C.

29. (Withdrawn) The process as claimed claim 19, characterized in that the proportion of macromolecular polyaldehyde to native collagen is between 1/10 and 1/50, preferably 1/10 to 1/30, and the mixing temperature is between 18°C and 37°C.

30. (Withdrawn) The process as claimed in claim 19, characterized in that the protein compound has been modified chemically or by oxidative cleavage beforehand, in particular by treatment with periodic acid or a salt thereof, and in that the polymerization agent consists of a buffer at slightly alkaline pH so as to allow the polymerization/crosslinking of the protein compound at an approximately neutral pH.

31. (Withdrawn) The process as claimed in claim 19, characterized in that it comprises mixing fibrinogen with thrombin, in aqueous solution.

32. (Withdrawn) The process as claimed in claim 19, characterized in that the gas is selected from air, nitrogen, oxygen and carbon dioxide or the mixture of one or more of these gases, preferably from air, carbon dioxide and nitrogen, air being most particularly preferred.

33. (Withdrawn) The process as claimed in claim 19, characterized in that the gas is combined with one or more of the constituents for the adhesive protein matrix.

34. (Withdrawn) The process as claimed in claim 19, characterized in that the gas is combined with a biocompatible and nontoxic vehicle, preferably formed from a protein compound which consists of, or comprises, a protein or a mixture of proteins selected from collagen, gelatin, albumin, elastin and fibrinogen, preferably from collagen and albumin.

35. (Withdrawn) The process as claimed in claim 19, characterized in that the gas is supplied with the aid of the polymerization/crosslinking agent and/or of the vehicle in pulverulent or lyophilized form.

36. (Withdrawn) The process as claimed in claim 19, characterized in that the gas is supplied with the aid of the protein compound in pulverulent or lyophilized form.

37. (Withdrawn) The process as claimed in claim 19, characterized in that the volume of gas introduced represents 25 to 90% of the total volume of the adhesive foam, preferably 40 to 75%.

38. (Withdrawn) The process as claimed in claim 19, characterized in that it comprises introducing one or more biologically active substances into the adhesive protein matrix material.

39. (Withdrawn) The process as claimed in claim 38, characterized in that the biologically active substance(s) is (are) combined with a biocompatible and nontoxic vehicle which is optionally the vehicle for the gas or the mixture of gases.

40. (Withdrawn) The process as claimed in claim 19, characterized in that the adhesive fluid protein foam is produced by transferring the mixture back and forward between two syringes.

41. (Withdrawn) The process as claimed in claim 19, characterized in that the gas is introduced into the adhesive matrix material (matrix in the process of forming).

42. (Withdrawn) The process as claimed in claim 19, characterized in that the gas is introduced at the time of mixing the constituents for the formation of the adhesive matrix.

43. (Withdrawn) The process as claimed in claim 19, characterized in that the gas is mixed with the adhesive matrix material so as to give a temperature of between 18°C and 41°C.

44. (Currently Amended) A kit for preparing a biocompatible fluid adhesive protein foam, which is bioresorbable and nontoxic, for surgical and/or therapeutic use, in particular for protecting/cicatrizing tissue wounds and attaching biological tissues to each other or an implanted biomaterial, said kit comprising:

- ~~a first container containing~~ a potentially adhesive protein compound which can be polymerized/crosslinked, solubilized in aqueous medium, ~~and, optionally, a biocompatible and nontoxic gas or mixture of gases~~ in a first container;
- ~~a second container containing~~ a polymerization/crosslinking agent for forming a biocompatible fluid adhesive protein matrix, which is bioresorbable and nontoxic, ~~and optionally, a biocompatible and nontoxic gas or mixture of gases~~ in a second container;

- ~~optionally a third container containing the whole or part of the~~ a biocompatible and nontoxic gas or mixture of gases, either in the first, second and/or a third container; ~~and~~

- optional means for extemporaneously mixing the constituents, protein compound in aqueous solution and polymerization/crosslinking agent for forming the adhesive matrix, and, ~~optionally, the~~ said gas or mixture of gases;

whereby the protein foam is obtained in a ready to use form.

45. (Previously Presented) The kit of claim 44, wherein the first container contains the potentially adhesive protein compound in pulverulent, dehydrated and optionally in a sterilized form, the second container contains an optionally sterile buffered aqueous solution, and wherein the kit further comprises means for supplying a polymerization/crosslinking agent to the solubilized protein compound and means for mixing the content of the first and second containers, and means for using a gas in the mixture and producing the foam.

46. (Previously Presented) The kit of claim 44, wherein the polymerization/crosslinking agent is a reactive polymer and the gas is selected from air, nitrogen, oxygen and carbon dioxide or the mixture of one or more of these gases.

47. (Previously Presented) The kit of claim 44, wherein the kit is in the form of two syringes equipped with mixing means, in which one of the syringes contains the protein compound in aqueous solution and the other contains the polymerization/crosslinking agent.

48. (Previously Presented) The kit of claim 44, wherein the gas is combined with the protein compound and/or with the polymerization/crosslinking agent.

49. (Previously Presented) The kit of claim 45, wherein the mixing means make it possible to pass the mixture from one syringe to the other several times so as to ensure the formation of the foam using the gas included in the syringe containing the pulverulent protein compound.

50. (Previously Presented) The kit of claim 44, wherein the gas is combined with a biocompatible and nontoxic vehicle.

51. (Previously Presented) The kit of claim 44, further comprising a third syringe containing the gas optionally combined with a vehicle.

52. (Previously Presented) The kit of claim 51, wherein the vehicle also contains one or more biologically active substances.

53. (Previously Presented) The kit of claim 44, wherein the polymerization/cross-linking agent and/or the vehicle is in lyophilized form.

54. (Previously Presented) A method for using a fluid adhesive protein foam as claimed in claim 1 for:

preventing or stopping the bleeding of vascular or tissue wounds;

attaching biological tissues including live tissues to each other or to an adjacent biomaterial;

cicatrizing surgical or chronic wounds;

protecting or sealing sutures;

preventing the formation of postoperative adhesions;

delivering biologically active substances for local application; and

filling tissue cavities.

55. (Previously Presented) The kit of claim 50, wherein biocompatible and nontoxic vehicle is formed from a protein compound which comprises a protein or a mixture of proteins selected from collagen, gelatin, albumin, elastin and fibrinogen.